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Minerva Anestesiologica 2021 December;87(12):1359-66
DOI: 10.23736/S0375-9393.21.15827-4

EXPERTS' OPINION

Tier-three therapies for refractory intracranial hypertension in adult head trauma

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ABSTRACT

Refractory intracranial hypertension after traumatic brain injury (TBI) is defined as recurrent increase of intracranial pressure above 20-22 mmHg for sustained period of time (10-15 min), despite conventional therapies, such as osmotic therapy, cerebral spinal fluid drainage and mild hyperventilation. As such, more aggressive treatments should be taken into consideration. In particular, therapeutic hypothermia, barbiturates administration and decompressive craniectomy are considered as tier-three or "salvage" interventions, as they have shown to be able to control refractory hypertension; however, they are also associated with an increased risk of significant side effects. Therefore, the aim of this review was to describe the evidence supporting the use of these tier-three therapies in the management of refractory intracranial hypertension in TBI patients.

(*Cite this article as:* Robba C, Iannuzzi F, Taccone FS. Tier-three therapies for refractory intracranial hypertension in adult head trauma. Minerva Anestesiol 2021;87:1359-66. DOI: 10.23736/S0375-9393.21.15827-4)

KEY WORDS: Brain injuries, traumatic; Barbiturates; Decompressive craniectomy; Hypothermia.

Increased intracranial pressure (ICP) is associated with poor outcome in traumatic brain injured (TBI) patients;[1-3] as such, early and aggressive treatment of intracranial hypertension (ICH) is fundamental to reduce secondary brain damage in TBI patients.[4-7]

In adult individuals, brain, blood and cerebrospinal fluid volumes remain constant and, being enclosed in a non-compliant skull, result in values generally below 10 mmHg. The pathophysiology of intracranial hypertension (ICH) after head trauma has been largely evaluated in both experimental and clinical studies and includes different mechanisms, such as brain edema, expanding mass, hyperemia due to loss of autoregulation, hypercapnia, hydrocephalus and increased intrathoracic or intra-abdominal pressure.[8] Intracranial hypertension has been traditionally defined as an ICP exceeding 20 mmHg;[9] however, the most recent Brain Trauma Foundation Guidelines have modified this threshold to 22 mmHg.[10] Importantly, these thresholds do not specifically indicate a trigger for therapy, as reduced cerebral blood flow and tissue hypoxia may occur even at lower ICP values.[11] However, as the risk of poor neurological recovery and early death increased when ICP remained above 20-22 mmHg for prolonged period of time, it is generally recommended to immediately initiate treatments aiming at reduce ICP in this setting,[9, 12] together with meticulous avoidance of systemic factors that can further raise ICP (*i.e.* hyponatremia, hypotension, anemia)[13] and a diagnostic workout to exclude new mass lesions that should be surgically evacuated.

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Initial stepwise approach for intracranial hypertension management

A number of ICP-lowering therapies have been evaluated and are currently applied in the clinical practice;[12] these strategies are generally used in a stepwise manner, with safer therapies being administered as first line interventions, and reserving more aggressive treatments, which are also associated with more side effects, for patients with persistent intracranial hypertension.

Severe (*i.e.* Glasgow Coma Scale [GCS]<9) TBI patients require ICP monitoring, early intubation and mechanical ventilation to protect airways and optimize gas exchanges, as well as sedation and analgesia to reduce pain and agitation.[13] Before starting any of ICP-lowering therapies, it is necessary to identify those extracerebral factors that contribute to ICH, such as obstructed venous return (*i.e.* head position or endotracheal tube necklace), hypoxemia, hypercapnia, fever, hypotension, hyponatremia, agitation, dysglycemia and anemia[1213]. Also, monitoring of electroencephalography (EEG) and/or initiation of an antiepileptic therapy could be considered.[12] These interventions are considered as "tier-zero" therapies, *i.e.* interventions that should be initiated in all severe TBI patients, independently from the presence of ICH (Figure 1).[14, 15]

In case of ICP>20-22 mmHg, brain imaging (*i.e.* cerebral CT scan) is often recommended to assess whether TBI patients necessitate a surgical intervention for mass-occupying space removal. Thereafter, "tier-one" therapies can be considered, which include: 1) increasing doses of sedation and analgesia; 2) administration of osmotic agents (*i.e.* mannitol or hypertonic saline); and 3) targeting partial pressure of carbon dioxide ($PaCO_2$) at lower ranges of normal values (*i.e.* 35-38 mmHg). Eventually, in case of

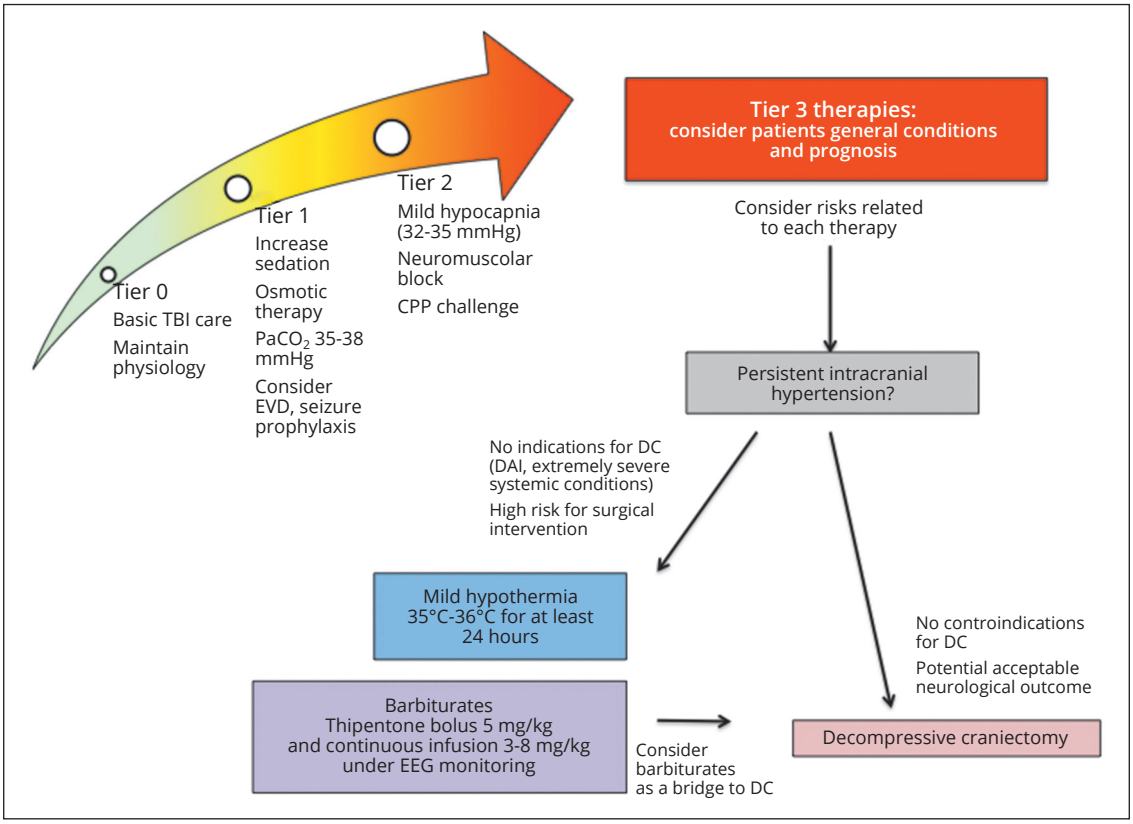
Tier 0
Basic TBI care
Maintain physiology
Tier 1
Increase sedation
Osmotic therapy
PaCO2 35-38 mmHg
Consider EVD, seizure prophylaxis
Tier 2
Mild hypocapnia (32-35 mmHg)
Neuromuscolar block
CPP challenge
Tier 3 therapies:
consider patients general conditions and prognosis
Consider risks related to each therapy
Persistent intracranial hypertension?
No indications for DC (DAI, extremely severe systemic conditions)
High risk for surgical intervention
Mild hypothermia 35°C-36°C for at least 24 hours
Barbiturates
Thipentone bolus 5 mg/kg and continuous infusion 3-8 mg/kg under EEG monitoring
Consider barbiturates as a bridge to DC
No controindications for DC
Potential acceptable neurological outcome
Decompressive craniectomy

Figure 1.—Staircase clinical approach to the use of tier-three therapies for the management of increased intracranial pressure. TBI: Traumatic brain injury; $PaCO_2$: partial pressure of carbon dioxide; CPP: cerebral perfusion pressure; DC: decompressive craniectomy; EEG: electroencephalography; EVD: external ventricular drain.

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persistent ICH, "tier-two" therapies can be initiated: 1) through the administration of neuromuscular blocking agents (NMBAs); 2) increasing cerebral perfusion pressure (CPP) by vasopressors (*i.e.* if autoregulation is intact, ICP will decrease): and 3) targeting mild hypocapnia (*i.e.* $PaCO_2$ 32-35 mmHg).[12]

Of note, among "tier-two" therapies, the use of NMBAs is effective only in some patients and probably related to the reduction of asynchronies with the ventilator and/or reduced carbon dioxide production from muscles. Also, controlled hyperventilation, which remains an effective and rapid intervention to reduce ICP in urgent situations (*i.e.* impelling herniation),[16] significantly reduces cerebral blood flow by arterial vasoconstriction, which might result, at least in case of profound hypocapnia (*i.e.* $PaCO_2$<30 mmHg) and prolonged use (>1 hour), in cerebral ischemia.[16, 17] As such, monitoring of the cerebral effects of hypocapnia (*i.e.* cerebral blood flow velocities using transcranial Doppler, brain oxygen pressure and/or cerebral microdialysis) could be useful to assess brain tolerance to this intervention and optimized $PaCO_2$ values.[17-19]

The role of "tier-three" therapies

In those patients (*i.e.* 10-15% of severe TBI) in whom all these therapies fail to reduce ICP,[20] "tier-three" therapies can be taken into consideration; these interventions include therapeutic hypothermia, barbiturates and decompressive craniectomy.[12]

Considering the significant side effects associated with each of these therapies and the lack of well-conducted randomized trials comparing tier-three interventions, the decision and initiate one of those should rely on the balance between risks and potential benefits, as well as the pathophysiology underlying refractory ICH (Table I).[21-25]

Therapeutic hypothermia

The neuroprotective effects of hypothermia are distinguished in ICP-dependent effects (*i.e.* which are mostly mediated by a reduction in cerebral metabolism, of the critical threshold for oxygen delivery and of blood volume, which is directly temperature dependent) and other effects, such as inhibition of excitoxicity and neu-

TABLE I.—*Type of "tier-three" therapy, mechanisms for ICP modulation, side effects and clinical recommendations.*

Type	ICP reduction	Side effects	Main RCTs	Clinical recommendation
Hypothermia	Decreases glucose consumption, cerebral metabolism and inflammatory response	Hemodynamic alterations, malignant arrhythmias, coagulopathy, infections.	Cooper *et al.*[21] Andrews *et al.*[22]	Early and prophylactic hypothermia are not recommended measures. Hypothermia can be used as tier 3 therapy when other measures are not effectives, according to patients' clinical status
Barbiturates	Depressing in cerebral function, metabolism and oxygen consumption	Hypotension, cardiological dysfunction, alteration in serum potassium levels, immunodepression, infections.	Eisenberg *et al.*[23]	Not recommended as prophylactic therapy, or in the early stages of ICP management. Barbiturates can be used as tier-three strategies, if DC is contraindicated, or as bridge for DC.
Decompressive craniectomy	Removing part of the skull provide additional space to the swollen brain reducing ICP	Intra-operative complication due to surgical procedures, infections, hemorrhage, seizure	Hutchinson *et al.*[24] Cooper *et al.*[25]	Early DC reduces ICP and ICU length of stay, but not improve outcomes as GOS-E score. Late DC can reduce mortality, but with possible worse effect on neurological outcome. Consider DC to reduce ICP if other therapies have been ineffective as tier 3 management.

ICP: Intracranial pressure; DC: decompressive craniectomy; ICU: Intensive Care Unit; GOS-E: Extended Glasgow Outcome Scale.

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ronal apoptosis, modulation of the inflammatory response, calcium antagonism and the reduction of cytotoxic oedema.[26] Main side effects are the impairment in cardiac function and risk of arrhythmias, altered coagulation and reduced platelets function, increased risk of infections, increased diuresis and electrolytes imbalances as well as hypovolemia.[26, 27]

The role of hypothermia in TBI patients is currently debated.[21, 22]

Some characteristics of experimental models (*i.e.* small animals; very early intervention; lack of comorbidities; inadequate long-term neurological assessment) might explain the discrepancies between the benefits of hypothermia animal studies on TBI and clinical evidence.[28] In one randomized controlled trial including 82 patients, an improvement of neurological outcome in TBI patients with GCS on admission of 5-7 was observed in those treated with hypothermia at 32 to 33 °C for 24 hours, when compared to normothermic patients.[29] In a second study, Clifton *et al.* randomized 46 TBI patients with GCS of 4-7 to normothermia (*i.e.* target body temperature of 37 °C) or hypothermia (*i.e.* 32 °C to 33 °C) and observed a significant reduction in seizure occurrence and an improvement in neurological function in patients who received hypothermia, without any increase in hemorrhagic coimplications.[30] However, these trials included a small number of patients and presented important methodological biases. Moreover, following studies conducted in USA using prophylactic hypothermia (*i.e.* 32-33 °C on admission for 48 hours), it is possible to observe no significant effects on mortality nor on neurological recovery in severe TBI patients.[31, 32] One recent study conducted in 511 severe TBI patients also confirmed the lack of any benefits from hypothermia when applied as early prophylactic treatment, and regardless of ICP values.[21] The EUROTHERM Study included 387 patients with increased ICP (*i.e.* >20 mmHg despite basic treatments, including sedation and mechanical ventilation) to receive either standard care (*i.e.* osmotic therapy, extra-ventricular drainage to remove cerebrospinal fluids, increased sedation, etc.) or hypothermia (*i.e.* 32-35 °C), which was adjusted on ICP values and could be used for a prolonged period of time. Not surprisingly, ICP was reduced in both groups and higher mortality was observed in the hypothermia group (odds ratio of 1.53; 95% confidence intervals 1.02 to 2.30; P=0.04) when compared to the normothermia group, in particular because of an increased number of systemic complications.[22, 33] Results from these trials suggest the hypothermia should not be used as early or prophylactic measure to control ICP; however, none of these studies challenged the role of hypothermia as "tier-three" therapy. Interestingly, targeting 35 to 35.5 °C can reduce ICH with similar results than lower temperatures, while maintaining sufficient cerebral perfusion pressure without cardiac dysfunction or tissue hypoxia.[34] As such, the use of mild hypothermia (*i.e.* 35-36 °C) *via* active cooling strategies is still recommended for the management of refractory ICH.[12]

Barbiturates

Barbiturates include a broad family of central nervous system depressants; among these, the most commonly used in TBI patients are pentobarbital and thiopental. Barbiturates have sedative, anesthetic and antiepileptic properties, and act by depressing cerebral function, decreasing cerebral blood flow and cerebral oxygen consumption, by reducing brain metabolism. The effects of cerebral hemodynamics and metabolism are more potent than other sedatives, such as propofol or midazolam, which translates into a more effective reduction of ICP.[35] Moreover, they can reduce pyruvate and lactate production and modulate neuronal GABA-regulation, resulting in neuronal hyperpolarization and inhibition of action potential (*i.e.* reduced epileptic threshold and excitotoxicity), as well as inhibit radical free mediated lipidic peroxidation.[35, 36] As the effects of barbiturates are not dose-dependent and present significant interindividual variability, continuous EEG monitoring should be used to identify the metabolic suppression of brain activity induced by these drugs; and no further increase in daily regimen should be therefore attempted in case of "burst-suppression" on EEG, as no additional ICP reduction would be obtained.[37]

The main side effects associated with barbiturates administration include hypotension, myocardial depression with consequent hemo-

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dynamic instability, reduction in immunity system function and drug accumulation, with a long half-life (up to 48 hours), resulting in prolonged alteration of consciousness and duration of mechanical ventilation.[23]

In one randomized controlled trial, high-dose barbiturates prevented ICP when added routinely to clinical management (*i.e.* ICP within normal values was observed in one third of cases assigned to the barbiturate group when compared with one sixth among those treated with standard strategies without barbiturate).[23] Importantly, most studies using barbiturates in TBI patients were performed when high-dose steroids, prophylactic hyperventilation and fluid restriction were considered as best practice in this setting;[38] as such, the generalizability of those findings to current TBI management is debatable, although it is commonly accepted that barbiturates should be no longer used as maintenance sedative agent in TBI patients.[39]

Decompressive craniectomy

The surgical management of ICH could be obtained by the evacuation of space-occupying lesions, drainage of cerebrospinal fluid and/or decompressive craniectomy (DC).[40] Decompressive craniectomy is a surgical procedure which consists in the removal of part of the skull and opening of the underlying dura mater, which can be performed either primarily (*i.e.* surgical evacuation of an extra-dural or subdural hematoma with the impossibility to close the skull after craniectomy because of extended brain swelling) or secondarily (*i.e.* refractory ICH, failing to "tier-one" and "tier-two" therapies).[11, 12, 41] Therefore, decompressive craniectomy can rapidly control ICP in severe TBI patients with refractory ICH by providing additional space to the swollen brain and minimizing the risk of brain herniation.[41]

A number of different techniques for DC have been described, which depend on location, type of injury and surgical approach, and can be summarized as: 1) bifrontal craniectomy; 2) unilateral hemicraniectomy; and 3) bilateral hemicraniectomy. Main complications associated with this neurosurgical procedure are infections, intracranial hemorrhage, seizures, transcranial herniation with cerebral injury, subdural hygroma and hydrocephalus.

Several observational studies have suggested a beneficial effect of DC on mortality and neurological outcome of severe TBI patients with refractory ICH,[42] with two randomized trials being published on this topic. The Decompressive Craniectomy (DECRA) study[25] evaluated the effects of bifrontal DC performed within 72 hours after TBI in case of intracranial hypertension, defined as ICP>20 mmHg for >15 minutes over 1-hour period, which was refractory to "tier-one" therapy. The group of patients which underwent DC had median lower ICP values than the group undergoing medical treatment; however, mortality rate was similar and the occurrence of unfavorable neurologic outcome higher among patients undergoing DC (70% *vs*. 51%; P=0.02) when compared to others. As such, DC should not be considered as an early treatment for ICP management, in particular before other potential medical interventions have not been initiated. More recently, the Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) study[24] compared DC and medical therapy (*i.e.* mainly barbiturates) in 408 patients with a sustained elevation in ICP above 25 mmHg for 1-12 hours and not responding to maximal medical therapy. Results from this trial suggested that DC could significantly decrease 6-month mortality (26.9% *vs*. 48.9%; P<0.001); also, despite a higher rates of unfavorable neurological outcome among survivors when compared to medical therapy, it has been estimated that for every 100 patients treated with DC rather than medical intent, 36% of the 22 additional patients who survived because of these intervention had lower cerebral disability. As such, surgical DC should be considered in patients with persistent refractory ICH, provided that adequate ethical considerations, which include age, frailty and pre-injury clinical conditions of the patients as well as a discussion with patients' relatives, are undertaken.

A practical approach

In the absence of clear indications and evidence supporting one intervention over the others, the

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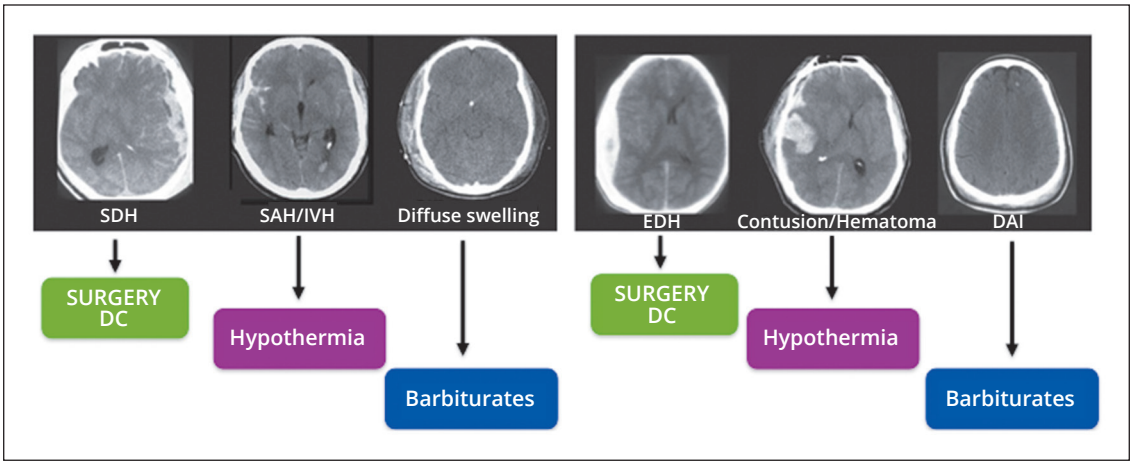

Figure 2.—Example of a practical approach for the decision to use tier-three therapies for the management of increased intracranial pressure according to different acute brain injuries.
SDH: Subdural hemorrhage; SAH: subarachnoid hemorrhage; IVH: intraventricular hemorrhage; DC: decompressive craniectomy; EDH: extradural hemorrhage; DAI: diffuse axonal injury.

decision of selecting hypothermia, barbiturates or DC should be based, in our opinion, on the pathophysiology of head trauma and ICH.

As an example, in case of refractory ICH associated with high-volume intracerebral hematomas requiring surgical drainage or cerebral contusion with large midline shift and/or brainstem herniation, DC should be the preferred method to control ICP (Figure 2). In these patients, barbiturates could be initiated as bridge to the operative room to minimize the risks of cerebral hypoperfusion. Moreover, barbiturates could be the first choice in case of diffuse axonal injury, to avoid bilateral craniectomy (*i.e.* high risk of complications), and because of hypothermia has been associated with an increased probability of poor outcome in this setting.[43] Finally, in case of ICH associated with contusional areas and mixed density injuries, in whom DC is contraindicated/denied or in the absence of large midline shift and brainstem herniation, hypothermia could be considered, as it would potentially minimize the occurrence of vasogenic edema (*i.e.* reduced permeability of the blood-brain barrier); moreover, it has been associated with a better outcome in this subgroup of patients.[29, 43]

Of course, this approach should be further validated and combination of different "tier-three" therapies could also be considered, although the risk of side effects would also significantly increase.

Conclusions

Management of refractory ICH is challenging, but a number of rescue or "tier-three" therapies can be used. These aggressive treatments may have several adverse effects and their use should be taken in consideration balancing risks and benefits. Despite high-quality evidence is lacking regarding the effects on outcomes of these interventions, their application is still recommended in selected TBI cases when other medical therapies have failed to control ICP within desired ranges.

Key messages

- Refractory intracranial hypertension is associated with increased mortality and poor neurological outcome after TBI; and should be aggressively treated.
- Tier-three therapies should be reserved to refractory cases of intracranial hypertension when other medical therapies have failed, as they can lead to important side effects.
- Hypothermia, barbiturates and decompressive craniectomy can all reduce ICP in this setting; how to select the best intervention according to the clinical scenario remains a matter of debate.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Chiara Robba and Francesca Iannuzzi have given substantial contributions to manuscript writing, Fabio S. Taccone to manuscript supervision and critical revision. All authors read and approved the final version of the manuscript.

Comment in: Gelormini C, Caricato A. "Tier-three" therapies in intracranial hypertension: is it worthwhile? Minerva Anestesiol 2021;87:1287-9. DOI: 10.23736/S0375-9393.21.16117-6.

History.—Article first published online: August 2, 2021. - Manuscript accepted: July 26, 2021. - Manuscript revised: July 19, 2021. - Manuscript received: April 30, 2021.

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